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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/031,342	03/26/2002	Torben Halkier	3631-0118P	6459

2292 7590 12/30/2004

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EXAMINER
BELYAVSKYI, MICHAIL A

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 12/30/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/031,342	HALKIER ET AL.	
	Examiner	Art Unit	
	Michail A Belyavskyi	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 September 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 53-104* is/are pending in the application.

4a) Of the above claim(s) *1,53-80 and 84-102* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *81-83,103 and 104* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment, filed 09/30/04 is acknowledged.

2. Claims 1 and 53-104 are pending.

3. Applicant's election without traverse of group VIII, claims 81-83, now claims 81-83 and 103-104 in the reply filed on 09/30/04 is acknowledged.

Claims 1, 53-80 and 84-102 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to nonelected inventions.

Claims 81-83 and 103-104 , read on a GDF-8 analogue, derived from animal GDF-8 polypeptide wherein said analogue has been modified by substituting at least one first amino acid in SEQ ID NO:12 with at least one second amino acid sequences which comprises a foreign T_H epitope wherein said first amino acid sequence is from residues 18 –41 of SEQ ID NO:12 are under consideration in the instant application.

4. The specification is objected to under 37 CFR 1.821(d) for failing to disclose SEQ ID NOS, for the amino acid sequence disclosed on page 25 , line 26.

It is also noted that the term " Fcγ " is misspelled on page 26, lines 10-15.

4. An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification or in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)).

5. The use of the trademark " ISCOM" has been noted in this application (for example on page 33, line 17). Each letter of the trademarks should be capitalized wherever it appears and be accompanied by the generic terminology.
Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

6. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention *to which the claims are directed.*

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 81-83 and 103 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a New Matter rejection**.

" ...wherein said first amino acid sequence is from one or more residues 1-12, 18 –41, 43-48, 49-69 or 79-104 of SEQ ID NO:12 " claimed in 81 and 103 represent a departure from the specification and the claims as originally filed and applicant has not pointed out where the support come(s) from. The specification and the claims as originally field only support " wherein said first amino acid sequence is from one of the residues 1-12, 18-30, 42-51, 82-86 and 105-109 ".

9. Also the issue is that Claims 81-83 and 103-104 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a GDF-8 analogue, derived from animal GDF-8 polypeptide wherein said analogue has been modified by substituting at least one first amino acid in SEQ ID NO:12 with at least one second amino acid sequences which comprises a foreign T_H epitope, wherein said T_H epitope is *Tetanus toxoid* epitope and wherein said first amino acid sequence is from on of residues 1-12, 18-30, 42-51, 82-86 and 105-109 " of SEQ ID NO:12 does not reasonably provide enablement for *any* GDF-8 analogue, derived from animal GDF-8 polypeptide wherein said analogue has been modified by substituting at least one first amino acid in SEQ ID NO:12 with at least one second amino acid sequences which comprises *any* foreign T_H epitope. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification does not enable one of skill in the art to practice the invention as claimed without undue experimentation.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, limited working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention.

The instant specification disclosed only a GDF-8 analogue, derived from animal GDF-8 polypeptide wherein said analogue has been modified by substituting at least one first amino acid in SEQ ID NO:12 with at least one second amino acid sequences which comprises a foreign T_H epitope, wherein said T_H epitope is *Tetanus toxoid* epitope and wherein said first amino acid sequence is from on of residues 1-12, 18-30, 42-51, 82-86 and 105-109 " of SEQ ID NO:12 (see overlapping pages 54-55 in particular). Applicant has not taught how to make and/or used *any* GDF-8 analogue, derived from animal GDF-8 polypeptide wherein said analogue has been modified by substituting at least one first amino acid in SEQ ID NO:12 with at least one second amino acid sequences which comprises *any* foreign T_H epitope that can be used to down regulate GDF-8 to increase muscle mass. The structural and functional characteristics of said peptides are not defined in the claim. Applicant acknowledge that only very limited number of promiscuous T_H epitopes are known and can be used in the resent invention (see page 13, lines 7-27 in particular). Applicant further acknowledge that not all variants or fragments of native GDF-8 polypeptide will have the ability to elicit antibody which are cross-reactive with the native form (see page 51, lines 4-8 in particular).

Colman *et al.*,(IDS) teach single amino acid changes in an antigen can effectively abolish antibody antigen binding. Abaza *et al.*, (IDS) teach that single amino acid substitutions outside the antigenic site on a protein effect antibody binding. Further, Lederman *et a., l* (IDS) disclose that a single amino acid substitution in a common allele ablates binding of a monoclonal antibody (see entire document). In addition, the current state of the art in epitope structure prediction is limited given the noncontiguous amino acid residues constitute most epitopes, and that the dynamics of binding is often not integrated into the epitope prediction equation, making epitope structure prediction a complex four-dimensional problem (see Van Regenmortel, IDS). Van Regenmortel notes that 90% of antibodies raised against intact proteins do not react with any peptide fragment derived from the parent protein indicating that these antibodies are directed to discontinuous epitopes (see page 466, column 1 in particular). In addition Van Regenmortel states that the low success rate of antigenic prediction is due to the fact that predictions concern only continuous epitopes and it is unrealistic to reduce the complexity of epitopes that always possess conformational features to one-dimensional, liner peptide models (see page 467, column 2 in particular). Detailed information regarding to how to make and use any *any* GDF-8 analogue, derived from animal GDF-8 polypeptide wherein said analogue has been modified by substituting at least one first amino acid in SEQ ID NO:12 with at least one second amino

acid sequences which comprises *any* foreign T_H epitope that can induces production of antibody against the GDF-8 polypeptide is lacking. Therefore, predicting which antibodies outside of the antibodies to a GDF-8 analogue, derived from animal GDF-8 polypeptide wherein said analogue has been modified by substituting at least one first amino acid in SEQ ID NO:12 with at least one second amino acid sequences which comprises a foreign T_H epitope, wherein said T_H epitope is *Tetanus toxoid* epitope and wherein said first amino acid sequence is from on of residues 1-12, 18-30, 42-51, 82-86 and 105-109 " of SEQ ID NO:12 is well outside the realm of routine experimentation. A skilled artisan would require guidance, such as information regarding the specific epitope recognition of the antibodies successfully used in the instant invention in a manner reasonably commensurate with the scope of the claims. Thus, it would require undue experimentation of one skilled in the art to practice the claimed invention.

Since the instant fact pattern fails to indicate that representative number of structurally related compounds is disclosed, the artisan would not know the identity of a reasonable number of representative compounds falling within the scope of the instant claims and consequently would not know how to make them. An assay for *finding* a product is not equivalent to a positive recitation of *how to make* a product.

The scope of the claimed *any* GDF-8 analogue, derived from animal GDF-8 polypeptide wherein said analogue has been modified by substituting at least one first amino acid in SEQ ID NO:12 with at least one second amino acid sequences which comprises *any* foreign T_H epitope is not commensurate with the enablement provided by the disclosure of a GDF-8 analogue, derived from animal GDF-8 polypeptide wherein said analogue has been modified by substituting at least one first amino acid in SEQ ID NO:12 with at least one second amino acid sequences which comprises a foreign T_H epitope, wherein said T_H epitope is *Tetanus toxoid* epitope and wherein said first amino acid sequence is from on of residues 1-12, 18-30, 42-51, 82-86 and 105-109 " of SEQ ID NO:12 with regard to the extremely large number of amino acid sequences broadly encompassed by the claimed invention. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's or peptide's amino acid sequence, and, in turn, nucleic acid sequence and still retain similar biological activity or structural specificity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the protein's structure relates to its function. However, the problem of predicting protein structure from mere sequence data of a limited number of proteins and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein and finally what changes can be tolerated with respect thereto is extremely complex and well outside the realm of routine experimentation.

Thus, Applicant has not provided sufficient guidance to enable one skill in the art to use claimed *any* GDF-8 analogue, derived from animal GDF-8 polypeptide wherein said analogue has been modified by substituting at least one first amino acid in SEQ ID NO:12 with at least one second amino acid sequences which comprises *any* foreign T_H epitope in manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement. *In re Fisher*, 166 USPQ 18(CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

In view of the quantity of experimentation necessary, the unpredictability of the art, the lack of sufficient guidance in the specification, the limited working examples, and the limited amount of direction provided given the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

10 . Claims 81-83, 103 and 104 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is in possession of : a GDF-8 analogue, derived from animal GDF-8 polypeptide wherein said analogue has been modified by substituting at least one first amino acid in SEQ ID NO:12 with at least one second amino acid sequences which comprises a foreign T_H epitope, wherein said T_H epitope is *Tetanus toxoid* epitope and wherein said first amino acid sequence is from on of residues 1-12, 18-30, 42-51, 82-86 and 105-109 " of SEQ ID NO:12.

Applicant is not in possession of : *any* GDF-8 analogue, derived from animal GDF-8 polypeptide wherein said analogue has been modified by substituting at least one first amino acid in SEQ ID NO:12 with at least one second amino acid sequences which comprises *any* foreign T_H epitope

The claimed invention is drawn to a genus of GDF-8 analogue derived from an animal GDF-8 that can be used to down regulate GDF-8. However, no structural or specific functional characteristics of such analogue is provided. The specification fails to define any *any* GDF-8 analogue derived from animal GDF-8 polypeptide wherein said analogue has been modified by substituting at least one first amino acid in SEQ ID NO:12 with at least one second amino acid sequences which comprises *any* foreign T_H epitope that can be used to down regulate GDF-8 polypeptide.

Applicant has disclosed a limited number of species; therefore, the skilled artisan cannot envision all the contemplated amino acid sequence possibilities recited in the instant claims. Consequently, conception in either case cannot be achieved until a representative description of

the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. The sequences themselves are required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993).

A description of a genus of protein sequences may be achieved by means of a recitation of a representative number of polypeptide sequences, defined by amino acid sequence, falling within the scope of the genus, or of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus. Regents of the University of California v. Eli Lilly&Co., 119F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> *(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.*

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

12. Claims81-83 and 103-104 are rejected under 35 U.S.C. 103(a) as being unpatentable over US. Pat. No. 6,369,201 (IDS) or US Patent 6607884 each in view of the known fact disclosed in the specification on pages 16, lines 24-30 and page 51, lines 7-15.

US Patent '201 teaches one GDF-8 or myostatin analogue, wherein myostatin is derived from animal and myostatin immunoconjugate comprising at least one myostatin analogue, linked to an immunological carrier (see Abstract and Column 4, especially lines 1-4; column 7 lines 15-22, column 9, lines 22-35, column 13, lines 1-5 in particular). It is noted that US Patent '201 teaches SEQ ID NO:2 that is 100 % identical to SEQ ID NO:12 of the instant application. (see attached sequence alignment). US Patent '201 teaches that the term "myostatin immunogen" includes polypeptide of myostatin molecule, analogue and modification by substitution such that a substantial fraction of myostatin B cell epitopes are preserved and do not affect the ability of the analog to induces an immunological response (see column 6, lines14-65, column 7, lines 6-15, column 15 lines 1-5, and column 16, lines 42-45 in particular). US Patent '201 teaches a myostatin multimer, wherein modification includes duplication of at least one myostatin B cell epitope (see column 7, lines 23-30 and column 8, lines 45-65 in particular). US Patent '201 further teach that in order to facilitate breaking of autotolerance to autoantigens myostatin molecule can be modified with foreign T_H epitope, such as *Tetanus toxoid* epitope (see column 9, lines 20-45).

US Patent '884 teaches GDF-8 or myostatin analogue, wherein myostatin is derived from animal and myostatin immunoconjugate comprising at least one myostatin analogue (see Abstract and Column 6 and column 8 in particular). It is noted that US Patent '884 teaches SEQ ID NO:21 that is 100 % identical to SEQ ID NO:12 of the instant application. (see attached sequence alignment). US Patent'884 teaches that GDF-8 analogue can be a minor modification including deletion or substitution which have substantially equivalent activity (see column 8 in particular). US Patent'884 teaches that is well known in the art that in order to increase immunogenicity GDF-8 analogue can be modified with foreign T_H epitope, such as *Tetanus toxoid* epitope (see column 12 in particular).

US Patent '201 and US Patent '884 does not explicitly teaches the particular modification of myostatin wherein said molecule has been modified so that at least one foreign T_H epitope moiety is introduced at amino acid from 18-41 of myostatin SEQ ID NO:12.

The Specification disclosed that it is well known in the art at the time the invention was made the existence of various methods of modifying a peptide self-antigen in order to obtain breaking of autotolerance, including introducing into said molecule at least one foreign T cell epitope such *Tetanus toxoid* (see page 16, lines 24-30 of the instant Specification in particular). The Specification further disclosed that it is not difficult to set up an effective standard screen for modified GDF-8 molecules which fulfils the minimum requirements for immunological reactivity (see page 51, lines 7-15 of the instant Specification in particular). In other words, Applicant acknowledge that it is within the skill in the art to identify the exact position for substitution with T_H epitope in myostatin molecule in order to increase immunogenicity of GDF-8 analogue and facilitates breaking of autotolerance of said molecule.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to apply the teaching of the known fact disclosed in the Specification on page 16, lines 24-30 and page 51, lines 7-15 to those of US Patent '201 or US Patent '884 to obtain the claimed GDF-8 analogue, derived from animal GDF-8 polypeptide wherein said analogue has been modified by substituting at least one first amino acid in SEQ ID NO:12 with at least one second amino acid sequences which comprises a foreign T_H epitope, wherein said T_H epitope is *Tetanus toxoid* epitope and wherein said first amino acid sequence is from residues 18-41 of SEQ ID NO:12.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so, because it is well known in the art that modifying a peptide self-antigen by introducing into said molecule at least one foreign T cell epitope (for example *Tetanus toxoid* epitope) will facilitate breaking of autotolerance, and that it is not difficult to set up an effective standard screen for modified GDF-8 molecules which fulfils the minimum requirements for immunological reactivity as taught by the Known fact disclosed in the Specification on pages 16 and 51. Said specific position of modified GDF-8 analogue can be applied to GDF-8 analogue taught by US Patent '201 or US Patent 884. Further, it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable positions involves only routine skill in the art. *In re Aller*, 220 F2d 454,456,105 USPQ 233; 235 (CCPA 1955). see MPEP § 2144.05 part II A.

From the combined teaching of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention and that it is within the skill in the art to identify the exact position for substitution with T_H epitope in myostatin molecule in order to increase immunogenicity of GDF-8 analogue and facilitates breaking of autotolerance of said molecule.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

13. No claim is allowed.

14. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which Applicant may become aware in the specification.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michail Belyavskyi whose telephone number is 571/272-0840. The examiner can normally be reached Monday through Friday from 9:00 AM to 5:30 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571/272-0841.

The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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